Dementia-associated mortality and its predictors among older adults in sub-Saharan Africa: results from a two-year follow-up in Congo (the EPIDEMCA-FU study).

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Abstract

Background: Between 2001 and 2012 we carried out a study of dementia prevalence in central Africa throughout the EPIDEMCA (Epidemiology of Dementia in Central Africa) programme.

Objective: To assess dementia related mortality among Congolese older people from the EPIDEMCA study after two years of follow-up.

Design: Longitudinal population-based cohort study.

Setting: Gamboma and Brazzaville, Republic of Congo.

Methods: Older participants were traced and interviewed in rural and urban Congo annually between 2012 and 2014. DSM-IV and NINCDS-ADRDA criteria were required for dementia diagnosis. Data on vital status were collected throughout the follow-up. Cox proportional hazards model was used to assess the link between baseline dementia diagnosis and mortality risk.

Results: Of 1,029 participants at baseline, 910 (88.4%) have a complete cognitive diagnosis. There were 791 participants (76.87%) with normal cognition, 56 (5.44%) with MCI, and 63 (6.12%) with dementia. After two years of follow-up, 101 (9.8%) participants had died. Compared to participants with normal cognition, mortality risk was more than 2.5 times higher among those with dementia (HR= 2.53, 95% CI: 1.42-4.49, p=0.001). Among those with dementia, only clinical severity of dementia was associated with an additional increased mortality risk (HR=1.91; CI 95%, 1.23-2.96; p=0.004). Age (per 5-year increase), male sex and living in an urban area were independently associated with increased mortality risk across the full cohort.

Conclusion: Among Congolese older adults, dementia is associated with increased mortality risk. Our results highlight the need for targeted health policies and strategies for dementia care in sub-Saharan Africa (SSA).

Keywords: Dementia, mortality, older adults, sub-Saharan Africa, Republic of Congo

Introduction

The African population is ageing at an unprecedented rate. Age-related diseases like dementia, including Alzheimer's disease (AD), are becoming a major public health issue [1]. It is estimated that 44.4 million people worldwide were living with dementia in 2013. This number is predicted to reach 75.6 million in 2030 and 135.5 million in 2050 [2]. The bulk of the projected increase in the number of people living with dementia will take place in Low and Middle Income Countries (LMIC), where over 70% of people with dementia are expected to live in 2040 [3]. This is in part due to rising numbers of people with dementia in sub-Saharan Africa (SSA) [4].

Longitudinal data suggest that dementia is associated with increased mortality risk [5 - 6 - 7]. Despite the magnitude of the situation, a low level of public understanding about dementia persists in LMIC and even more in SSA. Mortality data are useful for understanding the epidemiology and disease burden of dementia, and studies investigating the association between dementia and mortality in Africa are therefore of value.

People suffering from dementia die considerably earlier than those without [8 - 9 - 10]. Reported survival time varies from three to ten years from the onset of symptoms or from diagnosis of dementia [11]. Within cohorts of people with dementia, age, male sex and disease severity are commonly associated with mortality risk [10].

To date, the only SSA countries where dementia-related mortality has been documented are Nigeria and Tanzania. These two studies report a dementia-related mortality risk of 2.83 after five years of follow-up and 6.33 after four years respectively among Yoruba older people with dementia and Tanzanian older people [5 - 12].

The EPIDEMCA-FU programme (Epidemiology of Dementia in Central Africa – Follow-Up) offers an opportunity to assess dementia-related mortality in a Congolese population-based cohort. At baseline, the crude prevalence was estimated at 5.67% (95% CI= 3.85 - 8.00) and 6.60% (95% CI= 4.58 - 9.04) respectively for Gamboma (rural area) and Brazzaville (urban area) [13].

In this survey, we assess the link between dementia and two-year mortality in the older people population of Congo. We also investigate which factors are predictors of mortality among people with dementia.

Methods

Study design and participants

Between 2011 and 2012, a population-based study of dementia prevalence and its associated factors in Central Africa (EPIDEMCA) was carried out [3]. Around 2,000 participants aged 65 and above living in Central African Republic (CAR) and Republic of Congo (ROC) were interviewed. The full protocol of the EPIDEMCA study (including data collection, variable definition and dementia diagnosis) has been described elsewhere [3]. In order to assess dementia-related mortality in this population, we designed the EPIDEMCA-FU study. Participants from EPIDEMCA were followed up for two years after the prevalence study. The two-year follow-up was limited to participants living in ROC. Unfortunately, due to the ongoing political crisis, follow-up of CAR participants was not feasible.

EPIDEMCA-FU followed up 1,029 participants aged 65 and above living in Congo between 2012 and 2014: 529 participants (51.4%) in Gamboma (rural) and 500 (48.6%) in Brazzaville (urban).

The whole cohort was followed up for two years after the initial assessment or until death if they died before the end of the study period. Information on vital status was obtained every year during the follow-up study. Dementia cases were all prevalent at baseline (i.e. diagnosed during the prevalence survey as no prior diagnosis of dementia was recorded).

Baseline data collection

At baseline, data were collected using a standardized questionnaire administered at home by trained investigators. All questions and tests were adapted, back-translated and pretested in the local languages (Lari, Lingala, and Kituba). The interview included items about sociodemographic characteristics (age ascertained by official documents, from an informant or through a local event calendar; sex; marital status; education level), physical health (hypertension, diabetes, nutritional status and peripheral artery disease), lifestyle (alcohol and tobacco consumption), depressive symptomatology (according to the Geriatric Mental State version B3 (GMS-AGECAT) [3], and a functional assessment.

Diagnostic procedure and criteria for dementia

Cognitive disorders were assessed at baseline through a two-phase screening and diagnostic procedure. The Community Screening Interview for Dementia (CSI-D) [14] was administered to identify suspected cases of dementia. All participants obtaining a poor performance on the CSI-D (COGSCORE $\leq$ 24.5) were referred for detailed clinical assessment with a neurologist. A neurological examination was performed, including history of stroke and depressive disorders (assessed by specific questions). Orientation skills and daily living activities were also investigated in order to evaluate dependence. Neurological assessments also employed additional cognitive tests: the Free and Cued Selective Reminding Test [15] (oral version with image), Zazzo's cancellation task [16] and Isaac's Set Test of verbal fluency [17]. During this phase, neurologists had access to participants' health booklets if available.

Dementia diagnosis was made according to the DSM-IV criteria [18] and AD was diagnosed according to the clinical criteria proposed by the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association) [19]. The severity of dementia was evaluated by the CDR (Clinical Dementia Rating Scale) [20]. Mild cognitive impairment (MCI) was diagnosed according to Petersen criteria [21]. An experienced neurologist reviewed all medical records and test performances for all the participants assessed at the second stage of the study in order to reach a consensus. In case of insufficient information to reach a diagnosis, the participant was coded unclassifiable.

Outcomes

The vital status of all participants two years after baseline diagnosis was assessed. In case of death a verbal autopsy with close relatives was performed. Date of death was recorded; if only the month of death was known, an arbitrary date set at the 15th of the month was assigned. The history of illness before death and probable cause of death were sought. We enquired whether subjects had died due to cardiovascular disease including stroke, cancer, infection, or other causes (accident, malaria, unknown cause, etc.). When we were unable to contact the participant, information on vital status was obtained from close relatives. When participants had moved away, we sought to contact them, even outside the study area. All participants for whom vital status could not be reliably confirmed were considered lost to follow-up.

Statistical analysis

Data were analysed using Stata software, version 10.1 (Stata-Corp, College Station, Texas, United States).

Baseline characteristics were compared using Chi^2 or Fisher's exact tests, where appropriate. The link between two-year mortality and dementia was examined using a multivariate Cox regression model, with estimations of hazard ratios (HR) and their 95% confidence intervals (CIs). The model was controlled for age, sex, residency area and comorbidities collected using Charlson's index [22]. This model was fitted using two-year vital status as the dependent variable. Independent variables were those collected during the baseline prevalence survey: age, sex, residency and other sociodemographic and clinical data. The confounding effects of covariates were examined individually in unadjusted Cox models. All covariates with a p value <0.20 in unadjusted Cox model were then selected and included in multivariate backward step-by-step regression model.

Similarly, we conducted a statistical analysis to assess factors associated with mortality in people with dementia. For this analysis, the model was fitted using vital status as the dependent variable. Cognitive status, age, sex, residency, hypertension, diabetes, ABI and global score of disease severity according to CDR scale were the covariate variables. The level of significance for all statistical analyses and multivariate models was fixed at 0.05.

Kaplan Meier curves were created according to diagnosis group in order to describe the impact of dementia on mortality using the date of the screening interview as the starting point and the date of death or two-year follow-up as the endpoint. Log rank tests were used to evaluate the equality of survival distribution for dementia.

Ethics

The study was approved by the Congolese ethical committee CERSSA (Comité d'Ethique de la Recherche en Sciences de Santé) and by an ethics review board (Comité de Protection des Personnes Sud-Ouest Outre Mer) in France.

Participants were recruited following informed consent from themselves and/or from relatives.

Results

Characteristics of participants

At baseline, the 1029 participants were aged from 65 to 99 years (mean age 73.8 ± 6.8 years), 403 (39.2%) were males and 626 (60.8%) females. Among those, 119 (11.6%) participants were excluded because of missing information concerning dementia diagnosis. Those were lost because of moving, death before diagnosis, refusal to participate in the second stage or unclassifiable after examination (n=8). The final study population included 910 participants (431 in Gamboma and 479 in Brazzaville). Excluded participants were more likely to be female (75.2 vs. 58.6%; p<0.001), widowed (68.1 vs 49.0, p=0.001), with lower levels of education (84.0 vs. 66.4, p<0.001) and rural residency (82.4 vs. 47.4%; p<0.001) (please see the table Appendix 1 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/). Very few participants were lost to follow-up (n=43, i.e.4.2%). No individuals with dementia were identified among the excluded participants.

Table 1 summarizes participant baseline characteristics according to cognitive status. People with dementia were older (p<0.001), more likely to be underweight (p=0.005), more likely to be widowed (p<0.001) and less likely to be alcohol consumers (p=0.012).

2-year mortality predictors

In unadjusted Cox analysis, mortality risk was associated with increasing age (5-year bands), sex, residency area, cognitive status, diabetes, peripheral artery disease, tobacco and alcohol consumption. After adjustment, the effect of diabetes, peripheral artery disease and tobacco consumption on the mortality risk disappeared (Table 2). The final model demonstrates a significant association between cognitive status and mortality risk. Mortality risk was more than two and a half times higher in the dementia group compared to those with normal

cognition (HR 2.53; CI 95% 1.42-4.49; p=0.001), but the risk increase was not statistically significant among those with MCI (HR 1.44, CI 95%, 0.65-3.18; p=0.367). Across the entire population, old age, male sex and living in an urban area were associated with an increased mortality risk, while moderate alcohol consumption was associated with decreased risk. Among those with dementia, only greater disease severity was strongly associated with increased mortality risk (global CDR score 0.5-1 vs $\geq$2) (HR 1.91; CI 95%, 1.23-2.96; p=0.004) (data not shown).

After two years of follow-up, 101 (11.6%) participants died and at least 16 deaths were related to cardiovascular diseases. Most of deaths (34.9%, p<0.001) occurred in the dementia group (please see the table Appendix 2 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/ for baseline characteristics). Kaplan-Meir curves were used to compare survival according to cognitive status (Figure 1). People with dementia had significantly shorter survival periods than those with MCI and normal cognition (log-rank test: p<0.001).

Discussion

In this population-based survey, dementia at baseline was associated with a 2.5 fold mortality risk, while MCI showed no association with mortality. Age, male sex and living in an urban area were also associated with mortality risk. When considering just people with dementia, only disease severity influenced mortality. Our findings are consistent with most studies highlighting the link between dementia and mortality [10], including previous results from Nigeria and Tanzania [5 - 12].

Dementia at baseline was associated with increased mortality risk, with an HR of 2.5. Previous studies have reported increasing mortality risk in dementia or AD, with HR ranging

from 1.4 [23] to 5.2 [24]. Among Yoruba older people in Nigeria, dementia was significantly associated with increased mortality risk, with an HR of 2.8 compared to those without [5]. In Tanzania, Paddick et al. found that after 4-years of follow-up dementia-related death risk was about 6.3 compared to those without [12]. Despite differences in study design and follow-up time, our results are consistent with these previous data. This suggests that dementia has an important impact on African older adults' mortality risk. In our study, MCI at baseline was not associated with increased mortality risk while in Tanzania MCI was associated to increased risk of death [12]. MCI is recognized as an intermediate stage of dementia [25]. Previous studies investigating the link between MCI and mortality have found contrasting results, sometimes observing significant positive associations [7 - 26] or sometimes no association [27]. In our study this may be due to a lack of statistical power due to the small number of participants with MCI (n=56) or to the short follow-up time.

Many factors have been reported to predict mortality in people with dementia. Age, sex, severity of disease and disability are the most commonly-reported factors [10 - 11]. In our study, only greater disease severity assessed by the CDR scale at baseline was associated with increased mortality risk in people with dementia. These findings are consistent with previous studies, which also reported this association [5 - 9 - 25 - 28]; however, greater disease severity has not always been found to increase mortality risk in people with dementia [28]. Within our study population, more than 70% of people with dementia who died during the follow-up had a global CDR score $\geq$ 2 at the time of diagnosis. High cognitive impairment at the time of dementia diagnosis probably contributed to an increased risk of death. These results should be considered with caution, because we did not identify other factors that might explain how disease severity can be associated with increased mortality among people with dementia.

People with dementia are heavy consumers of health services [29]. Those with a high disease severity need greater medical care and human assistance because of their dependence. In

ROC, as in most of LMIC, affected persons do not seek help; even if they do, health-care services tend not to meet their needs. For people with advanced dementia this situation may enhance global health deterioration and result in increased mortality risk. Guehne and colleagues [30] observed that the positive correlation between dementia severity and mortality was generally reported in studies carried out over at least 5 years. Report of positive association between disease severity and mortality just after 2 years of follow up, may be explained by the lack of adequate health care and also by the use of prevalent cases. These findings encourage the assumption that analyses of dementia mortality may be biased by the inclusion of more severe cases – usually older, with more comorbidities – who have a higher risk of death [7 - 14].

Limits of the study

We have studied a fairly large cohort of older adults and followed them up for two years. Unfortunately, more than ten percent of our baseline population was excluded due to missing data on dementia diagnosis. This is one of the main limits of two-phase design in dementia diagnosis. The delay between screening and diagnosis increased the number of participants lost to follow-up and the number of refusals, reducing our study population and probably affecting the power of our study. The lack of statistical power might have led to an underestimation of potential relationships between variables and dementia-related mortality. However, it is important to emphasize the high quality methodology used for diagnosing dementia cases, and the low rate of loss to follow-up two years after baseline. It would have been interesting to explore the impact of mortality according to dementia subtype; however, the lack of imaging for diagnosing dementia subtypes somewhat limited the appreciation of the various subtypes.

Conclusion

In this population-based cohort of older adults from ROC, dementia was associated with increased mortality among older adults. Among people with dementia, disease severity was strongly associated with increased mortality risk. These results highlight the contribution of dementia to older adult mortality. It is therefore important to manage this condition if we are to avoid premature risk of death in SSA.

Conflict of interest statement:

The authors declare that there is no conflict of interest associated with this manuscript.

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Authors' contributions

All the authors were involved in the study design. HS, BNB, PMB, MG, PL and JFD were involved on data collection. HS carried out the data analysis supported by MG and PL. HS and MG prepared the first draft. All the authors reviewed the manuscript, provided further contributions and suggestions. All the authors read and approved the final manuscript.

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374 Table 1: Baseline characteristics of 910 included participants according to cognitive status, EPIDEMCA-FU
375 2012-2014

	Dementia		MCI		Normal		Total		*P* value
	n	%	n	%	n	%	n	%	
Sociodemographic characteristics									
Age (year)									<0.001
[65-70[	9	14.29	11	19.64	286	36.16	306	33.63	
[70-75[	8	12.70	14	25.00	210	26.55	232	25.49	
[75-80[	12	19.05	19	33.93	151	19.09	182	20.0	
[80-85[	13	20.63	7	12.50	103	13.02	123	13.52	
≥85	21	33.33	5	8.93	41	5.18	67	7.36	
Sex [a]									<0.001
Women	49	77.78	45	80.36	439	55.50	533	58.57	
Marital status [b]									<0.001
Single	2	3.23	1	1.79	20	2.53	23	2.54	
Married	13	20.97	10	17.86	345	43.73	368	40.57	
Widowed	43	69.35	38	67.86	363	46.01	444	48.95	
Divorced	4	6.45	7	12.50	61	7.73	72	7.49	
Education [b]									0.002
No formal education	53	85.48	49	87.50	500	63.37	602	66.37	
Has not completed primary education	5	8.06	5	8.93	134	16.98	144	15.88	
Primary	2	3.23	1	1.79	78	9.89	81	8.93	
Secondary	1	1.61	1	1.79	41	5.20	43	4.74	
High	1	1.61	0	0.00	36	4.56	37	4.08	
Residency area [a]									0.199
Gamboma (rural)	30	47.62	33	58.93	368	46.52	431	47.36	
Death [a b]	22	34.92	7	12.50	72	9.56	101	11.58	<0.001
Probable Causes of death [b]									0.561
CVD	12	80.00	2	66.67	24	54.55	38	61.29	
Infectious	2	13.33	0	0.00	10	22.73	12	19.35	
Cancer	0	0.00	0	0.00	5	11.36	5	8.06	
Others	1	6.67	1	33.33	5	11.36	7	11.30	
Clinical characteristics									
Hypertension [a b]	41	67.21	34	60.71	244	31.08	616	68.29	0.436
Diabetes [a b]	4	6.56	5	8.93	92	11.87	101	11.32	0.381
ABI [b]									0.347
ABI≤0.9	10	24.39	11	21.15	117	15.94	138	16.69	
0.9<ABI<1.4	29	70.73	40	76.92	595	81.06	664	80.29	
ABI ≥ 1.4	2	4.88	1	1.92	2	4.88	25	3.02	
BMI (Kg/m2) [b]									0.005
<18.5	23	52.27	21	42.00	208	27.48	252	29.61	
18.5≤ BMI≤ 24.9	16	36.36	25	50.00	384	50.73	425	49.94	
25.0≤ BMI≤	4	9.09	3	6.00	106	14.00	113	13.28	

29.9									
≥30	1	2.27	1	2.00	59	7.79	61	7.17	
Life habits									
Tobacco consumption [b]									0.372
Never	50	80.65	40	71.43	643	81.70	733	80.99	
Former	4	6.45	4	7.14	48	6.10	56	6.19	
Current	8	12.90	12	21.43	96	12.20	116	12.82	
Alcohol consumption [b]									0.012
Never	53	96.36	51	91.07	635	80.89	739	82.48	
Sometimes	1	1.82	1	1.79	38	4.85	40	4.46	
Regularly	1	1.82	4	13.79	112	14.27	117	13.06	

376 [a]: omitted category for dichotomic variables

377 [b]: denominator may vary due to missing data

378 ABI: Ankle Brachial Index, BMI: Body Mass Index, CVD: Cardiovascular Disease, MCI: Middle Cognitive
379 Impairment

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381

382 Table 2: Two-year mortality associated risk factors, EPIDEMCA-FU 2012-2014

	Unadjusted cox analysis			Adjusted cox multivariate analyses (Final model) [C]		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age (for a 5 years increase)						
[65-70[	1	Reference		1	Reference	
[70-75[	0.98	0.53 - 1.89		0.93	0.49 - 1.77	0.833
[75-80[	0.93	0.53 - 2.00	<0.001	0.99	0.50 - 1.97	0.986
[80-85[	1.91	1.91 - 5.82		3.13	1.75 - 5.61	<0.001
>85	2.30	2.30 - 7.98		3.15	1.58 - 6.28	0.001
Sex						
Women	1	Reference		3.15	1.58 - 6.28	0.001
Men	1.65	1.11 - 2.46	0.012	2.31	1.52 - 3.50	<0.001
Cognitive status						
Normal	1	Reference		1	Reference	
MCI	1.31	0.60 - 2.84	<0.0	1.44	0.65 - 3.18	0.367
Dementia	3.87	2.36 - 6.34	01	2.53	1.42 - 4.49	0.001
Residence area						
Gamboma (rural)	1	Reference		1	Reference	
Brazzaville (urban)	1.43	0.95 - 2.14	0.080	1.62	1.06 - 2.45	0.023
Education						
No formal education	1	Reference				
Has not completed primary education	1.04	0.59 - 1.82				
Primary	1.44	0.76 - 2.65	0.874			
Secondary	0.92	0.36 - 2.37				
High	1.08	0.42 - 2.81				
Ankle Brachial index						
No artery disease	1	Reference				
Peripheral artery disease	1.97	1.19 - 3.28	0.043			
Mediacalcosis	1.01	0.24 - 4.16				
BMI (Kg/m2)						
<18.5	1	Reference				
18.5≤ BMI≤ 24.9	0.57	0.34 - 0.94	0.739			
25.0≤ BMI≤ 29.9	0.98	0.52 - 1.85				
≥ 30	0.87	0.38 - 1.98				
Hypertension						
No	1	Reference				
Yes	1.16	0.75 - 1.81	0.480			

Diabete						
No	1	Reference				
Yes	1.49	0.86 - 2.59	0.171			
Tobacco consumption						
Never smoked	1	Reference				
Former smoker	0.94	0.40 - 2.19	0.241			
Current smoker	0.64	0.34 - 1.33				
Alcohol consumption						
Never smoked	1	Reference		1	Reference	
Sometimes	0.65	0.20 - 2.07	0.053	0.58	0.18 - 1.89	0.374
Regularly	0.41	0.18 - 0.96		0.36	0.15 - 0.86	0.022

383 [c] adjusted for sex, age, residency area, cognitive status, ankle brachial index, alcohol use, and diabetes

384 HR: Hazard Ratio, CI: Confidence Interval, ABI: Ankle brachial Index, BMI: Body Mass Index MCI:
385 Middle Cognitive Impairment

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Figure 1: Survival curves for all-cause mortality at two-years according to dementia diagnosis group, EPIDEMCA-FU 2012-2014